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The following papers have been filed:

SUBMISSION OF ORIGINAL DECLARATION UNDER 37 C.F.R. §1.132 W/ORIGINAL SIGNED DECLARATION (MCALLISTER)

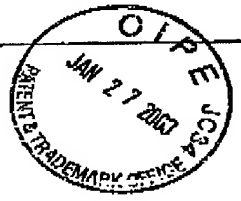
Name of Applicant: Valerie CHEYNET-SAUVION et al.

Serial No.: 09/402,131

Atty. File No.: 104458

Title (New Cases):

Sender's Initials: WPB/SXT:amw



164/38

PATENT OFFICE DATE STAMP

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PATENT APPLICATION

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re the Application of

Valerie CHEYNET-SAUVION et al. Group Art Unit: 1655

Application No.: 09/402,131 Examiner: B. Sisson

Filed: December 8, 1999 Docket No.: 104458

For: RNA-DEPENDENT RNA POLYMERASE FUNCTIONING PREFERABLY ON RNA MATRIX AND PROMOTER-DEPENDENT TRANSCRIPTION PROCESS WITH SAID RNA-DEPENDENT RNA POLYMERASE

DECLARATION UNDER 37 C.F.R. §1.132

Director of the U.S. Patent and Trademark Office
Washington, D.C. 20231

Sir:

I, William T. McAllister, a citizen of the United States of America, hereby declare and state:

1. My qualifications are set forth in the attached curriculum vitae.

2. I am an inventor of the above-identified patent application.

3. I am familiar with its contents and the contents of the pending Office Action and the accompanying Amendment After Final Rejection under 37 C.F.R. 1.116.

4. I have read and understand the attached references, and believe that the teachings of the attached references represent the state of the art at the time the application was filed. I believe that the specification as originally filed fully enabled one skilled in the art to make and use the invention as recited in the claims as amended by the accompanying Amendment After Final Rejection for the reasons set forth below.

5. One skilled in the art would have understood that RNA polymerases encoded by bacteriophage T7 and its relatives have many common structural and functional features.

The promoter sequences recognized by these phage polymerases, such as T7, T3, K11, SP6 and BA14 phage polymerases, all share a common 23 bp consensus sequence between nucleotides -17 to +6 (see e.g., McAllister, *Cellular and Molecular Biology Research* (1993) 39: 385-391). Because of the structural and functional similarities of the RNA polymerase encoded by these bacteriophages those skilled in the art refer to these RNA polymerases as "T7-like RNA polymerases" and to the phages as "T7-like bacteriophages." (See e.g., Chamberlin et al. (copy submitted with June 5, 2001, Amendment) at page 88, first paragraph, and page 89, Heading 11). Thus, referring to the RNA polymerase as "T7-like phage polymerase" would clearly have been understood by one skilled in the art as referring to the RNA polymerases encoded by T7 and its related phages.

6. In addition to recognizing this consensus sequence within the transcription promoter sequence, T7-like phage RNA polymerases also have a common organization. It is known in the art that these RNA polymerases consist of a single subunit (see e.g., Severinov, PNAS, (2000) 98: 5-7; Tahirov et al., Nature (2002) 420:43-50; and Yin et al., Science (2002) 298: 1387-1395). These references show that there are two "families" of DNA-dependent RNA polymerases that are recognized in the art. One family of polymerases encompasses the T7-like phage polymerases, which consist of a single subunit, while the second family of RNA polymerases covers bacterial and eukaryotic RNA polymerases, which consist of multiple subunits. As described in the specification at, for example, page 4, line 30 to page 53, the T7-like phage polymerases are an art-recognized class of very homologous enzymes. This is also supported by the discussion in Chamberlin et al., from page 89 to 91. Furthermore, Severinov, Tahirov et al. and Yin et al. further demonstrate and confirm the accuracy of this grouping of phage RNA polymerases. Thus, those skilled in the art would have recognized that the T7-like phage polymerases are a closely related group of RNA polymerases.

7. The ability to synthesize a polymer of nucleotides is conferred by the active site of the enzyme, which is highly conserved among the T7-like phage polymerases. An alignment of the RNA polymerases from exemplary T7, T3, SP6 and K11 RNA polymerases is attached. The alignment shows that the amino acid sequence from residue 620 to about 640 is highly conserved across the different types of T7-like phage polymerases.

8. The conserved amino acid sequence in this region of the T7-like phage RNA polymerases would also have suggested to one skilled in the art that similar changes made in the phage polymerases would result in the same or similar mutant phenotypes. Thus, one skilled in the art would have reasonably expected that a mutation at R627 in the manner described in the specification with respect to T7 RNA polymerase would result in a similar mutant phenotype as that of the T7 RNA polymerase in other T7-like phage polymerases. It is a generally accepted and routine practice among those skilled in the art to compare the amino acid sequence of related proteins to localize areas of importance and interest.

9. The skilled artisan would have determined an appropriate mutagenesis strategy based on the comparison of the amino acid sequences and structures. Thus, there would have been no need for the skilled artisan to examine multiple mutations at every possible position within the protein as asserted in the Office Action. The demonstration of one mutant of T7 RNA polymerase activity within a highly conserved region of the amino acid sequence shared by the T7-like phage RNA polymerases would have been expected to yield similar results in other T7-like phage polymerases. Thus, no undue experimentation would have been necessary to practice the claimed invention with various alternative T7-like phage polymerases.

10. The specification describes the modification of a T7 RNA polymerase at residue R627. As a result of this modification, the RNA dependent RNA polymerase activity of T7 RNA polymerase is greatly enhanced. As discussed above, this particular residu lies

within the highly conserved region, between amino acid residues 620 to about 640, that is shared by the T7-like phage RNA polymerases. Thus, one skilled in the art would have expected that the same or similar modification in the highly conserved regions within a different, but related, T7-like phage RNA polymerase would also enhance the RNA dependent RNA polymerase activity in the related T7-like phage RNA polymerase.

11. Thus, in view of the attached references, the specification as filed provides a fully enabling disclosure for the claimed invention. One skilled in the art would not have required further guidance or examples, nor would undue experimentation have been required to practice the claimed invention beyond what is disclosed in the specification.

12. I hereby declare that all statements made herein of my own knowledge are true, and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine and/or imprisonment under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing therefrom.

Date: 1/21/03

William T. McAllister

CURRICULUM VITAE

WILLIAM T. MCALLISTER

PRESENT POSITION:

Professor and Chairman
Department of Microbiology and Immunology
SUNY Health Sciences Center at Brooklyn, Brooklyn, NY

PERSONAL DATA:

Date of Birth: April 25, 1944
Three children: Elliot, Suzanne, Robert

EDUCATION:

1961-66	Lehigh University, Bethlehem, PA B.A. (Biology)
1966-67	Department of Microbial and Molecular Biology University of Pittsburgh, Laboratory of Dr. D. MacDonald Green
1967-70	Department of Biochemistry University of New Hampshire, Ph.D. (Biochemistry) Laboratory of Dr. MacDonald Green (genetics and biology of *B.subtilis* phages)
1970-72	Institute for Molecular Genetics Heidelberg University, Germany NIH Postdoctoral Fellow Laboratory of Dr. E.K.F. Bautz (molecular genetics, control of transcription)

PROFESSIONAL EXPERIENCE:

1966-67	Teaching Assistant, Department of Microbial and MolecularBiology University of Pittsburgh
1967-70	Research Assistant/Predoctoral Trainee, Department of Biochemistry, University of New Hampshire
1970-72	NIH Postdoctoral Fellow, Institute for Molecular Genetics Heidelberg University
1972-73	Research Associate, Institute for Molecular Genetics Heidelberg University

12/31/02

1973-79	Assistant Professor, Department of Microbiology, College of Medicine and Dentistry f New Jersey-Rutgers Medical School, Piscataway, New Jersey
1979-85	Associate Professor, Department of Microbiology, University of Medicine and Dentistry of New Jersey-Rutgers Medical School, Piscataway, New Jersey
1985-86	Professor, Department of Microbiology, University of Medicine and Dentistry of New Jersey-Rutgers Medical School, Piscataway, New Jersey
1986-	Professor and Chairman, Department of Microbiology and Immunology, State University of New York Health Sciences Center at Brooklyn, Brooklyn, NY

HONORS AND AWARDS:

Chancellor's Award for Excellence in Scholarship and Creative Activities, State University of New York, 2002

National Lecturer, American Society for Microbiology, 1986-87

Excellence in Teaching Award, Foundation of UMDNJ, Rutgers Medical School, 1980

Councilor, Harvey Society, 1987-1992

Chair, Division M (Bacteriophages), American Society for Microbiology, 1991-1992

Councilor, Association of Medical School Microbiology Chairs, 1994-1997

Faculty GEM Award for Outstanding Research, Alumni Association, College of Medicine, Downstate Medical Center, Brooklyn, NY 2001

RESEARCH SUPPORT:

Current:

NIH GM38147 "RNA polymerase structure and function", 12/01/98-11/30/02, Principal Investigator, Total project, $1,748,299; current year, $421,862.

Howard Hughes Medical Institute "Structure-function relationships of bacteriophage T7 RNA polymerase", 7/1/95-6/30/01. This is a collaborative project with Dr. Sergei Kochetkov, Moscow; I am the Lead Collaborating Scientist. Direct costs (to US laboratory): total project, $14,000; current year, $2,800.

Prior:

bioMerieux, S.A. "RNA polymerases with altered specificities", 7/1/93-6/30/98, Principal Investigator.

Life Technologies, Inc. "Development of phage RNA polymerase-based expression system", 7/1/92-6/30/94, Principal Investigator.

NIH-GM21783 "Regulation of viral gene expression", 07/01/74-6/30/88, Principal Investigator.

NIH AM-28561, "Folate binders, hematopoiesis, and cell replication", 6/1/87-5/31/92, Co-investigator.

New Jersey Commission on Cancer Research, 86-187-CCR, "Studies of recombination in papillomavirus-transformed cells", 07/01/86-6/30/87, Principal Investigator

NSF 412-6200A, "Support for an international workshop on gene organization and expression in bacteriophages", 7/1/88-6/30/89, Principal Investigator

NSF MCB9802092, "Support of an International Workshop on Macromolecular Interactions in Bacteriophages", 7/1/96-6/30/97, Principal Investigator

Pharmacia P-L Biochemicals, Inc, "Cloning and expression of the bacteriophage SP6 RNA polymerase gene", 01/01/87-12/31/90, Principal Investigator

Life Technologies, Inc., "Development of phage RNA polymerase-based expression systems", 01/01/91-12/31//94, Principal Investigator

Biotechnology Research and Development Corporation "Development of a plant expression system based upon phage T3 RNA polymerase", 4/1/92-8/31/93, Principal Investigator

PUBLICATIONS

Articles:

1. McAllister, W.T. (1970). Bacteriophage infection: Which end of the SP82G genome goes in first? J. Virology 5:194-198.

2. McAllister, W.T., and Green, D.M. (1972). Bacteriophage SP82G inhibition of an intracellular deoxyribonucleic acid inactivation process in Bacillus subtilis. J. Virology 10:51-59.

3. McAllister, W.T., and Green, D.M. (1973). Effects of the decay of incorporated radioactive phosphorus on the transfer of the bacteriophage SP82G genome. J. Virology 12: 300-309.

4. Dunn, J.J., McAllister, W.T., and Bautz, E.K.F. (1972). In vitro transcription of T3 DNA by E. coli and T3 RNA polymerases. Virology 48:112-125.

5. Dunn, J.J., McAllister, W.T., and Bautz, E.K.F. (1972). Transcription in vitro of T3 DNA by E. coli and T3 RNA polymerases II. Analysis of the products in a cell-free protein-synthesizing system. Eur. J. Biochem. 29:500-508.

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8. Kupper, H., McAllister, W.T., and Bautz, E.K.F. (1973). Comparison of E. coli and T3 RNA polymerases: Differential inhibition of transcription by various drugs. Eur. J. Biochem. 38:591-586.

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16. McCarron, R.J., and McAllister, W.T. (1978). Effect of ribosomal loading on the structural stability of bacteriophage T7 early messenger RNAs. Biochem. Biophys. Res. Commun. 80:789-796.

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PATENT APPLICATIONS:

Issued:

1. Highly efficient dual T7/T3 promoter vector pJKF16 and dual SP6/T3 promoter vector pJFK15. US Patent No: 5,017,488 (May 21, 1991) William T. McAllister, John F. Klement.

2. Plasmid for the overproduction of bacteriophage T3 RNA polymerase, transcription vectors that carry a promoter recognized by its polymerase, gene coding for T3 RNA polymerase and application of these plasmids. US Patent No:5,037,045 (August 6, 1991), William T. McAllister.

3. Gene coding for a protein having T3 polymerase activity. US Patent No: 5,102,802 (April 7, 1992) William T. McAllister.

4. Method of producing a gene cassette coding for polypeptides with repeating amino acid sequences. US Patent No: 57089,406 (February 8, 1992) Jon L. Williams, Anthony J. Salerno, Ina Goldberg, and William T. McAllister.

5. Chimeric oligonucleotides and their use in the production of transcripts from nucleic acids. European Patent No. EP 0721988 (7/17/96) , Guillou-Bonnid, F, Levasseur, P., Cleuziat, P., McAllister, W.T., and Mallet, F., (bioMerieux, S.A.)

6. RNA-dependent RNA polymerase functioning preferably on a RNA matrix and promoter-dependent transcription process with said RNA-dependent RNA polymerase. US patent PCT/FR98/00635 (3/27/98). Chaynet-Sauvon, V., Arnaud-Barbe, N., Oriol, G., McAllister, W.T., Mandrand, B., Mallet, F. (bioMerieux, S.A.)

Disclosures:

1. Cloning and expression of the bacteriophage SP6 RNA polymerase g n and vectors for its use. (June 23, 1988) William T. McAllister, Russell Durbin, Steven Risman.

2. Expression of foreign genes in mammalian cells under the control of the bacteriophage T3 RNA polymerase. (January 3, 1989) William T. McAllister, Youwen Zhou.

3. Regulated transcription system based upon the bacteriophage T3 RNA polymerase and lactose repressor. (January 6, 1989) William T. McAllister, Thomas Giordano.

4. Development of a stable mouse cell line that expresses bacteriophage T3 RNA polymerase in the cytoplasm. (January 12, 1989) William T. McAllister, Thomas Giordano, Youwen Zhou.

5. Multipurpose cloning vector for expression of foreign genes in prokaryotic and eukaryotic cells under the control of the bacteriophage T3 RNA polymerase. (May 31, 1989) William T. McAllister, Russell K. Durbin.

6. T7 RNA polymerase mutants with altered promoter specificities. (May 4, 1992) William T. McAllister, Curtis A. Raskin.

7. Phage RNA polymerase expression vectors that allow efficient expression of cloned genes in both prokaryotic and eukaryotic cells. (February 2, 1995) Biao He, Russell K. Durbin, William T. McAllister

8. Improved T7 and T3 RNA polymerases having greater processivity. (April 14, 1993) Lynn MacDonald, John J. Dunn, William T. McAllister.

9. Phage RNA polymerases with relaxed specificity. (November 16, 1993) William T. McAllister, Russell K. Durbin, Curtis A. Raskin, George Diaz, Frederic R. Bloom, Jhy-Jhu Lin.

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